Systematic literature review of basal bolus insulin analogue therapy during pregnancy

Abstract

Currently standard insulin therapy for pregnancies complicated by diabetes mellitus (DM) is a combination of intermediate Neutral Protamine Hagedorn (NPH) and regular human insulin. In contrast, for non-pregnant individuals with diabetes, standard insulin therapy is basal bolus therapy (BBT) using a combination of rapid- and long-acting insulin analogues designed to mimic physiologic biphasic insulin secretion by the pancreatic beta cells. Although there are published reports describing use of BBT during pregnancy, due to the lack of strong clinical evidence regarding safety and efficacy of BBT during pregnancy, its use has not been adopted as standard insulin administration during pregnancies complicated by diabetes mellitus. To evaluate the evidence for this discrepant clinical management, we conducted a systematic review. Search strategy and selection criteria: PubMed, Medline, Cochrane Database of Systematic Reviews for publications between 1996 and 2014. Search terms: lispro, apart, glargine, detemir, glulisine, Humalog, NovoLog, Lantus, Levemir, Apidra, pregnancy, and diabetes. Included: randomized clinical trials, prospective and retrospective cohort analyses, case-control studies and case series and reports. Search limited to human studies and English language. Excluded: review articles. Nineteen studies were identified that assessed safety/efficacy of rapid-acting insulin analogues, lispro and aspart, and 23 studies that assessed the long-acting insulin analogues, glargine and detemir, in pregnant patients complicated with pregestational (PGDM) and gestational diabetes mellitus (GDM). The principal efficacy endpoint examined in the selected studies was glycated hemoglobin levels. Other study outcome variables to assess maternal glycemic control included fasting and postprandial glucose levels, large for gestational age (LGA) infants, mean birth weight, congenital malformations, and incidence of hypoglycemic events. Compared to conventional insulin therapy, insulin analogue use provided similar overall glycemic control in pregnancy. In addition, they contributed to greater postprandial glucose control. There was no compelling evidence that insulin analogue use was associated with any significant differences in maternal and neonatal outcomes, particularly in terms of incidences in maternal and neonatal hypoglycemia, LGA, and congenital malformations. Given the documented benefits of physiological insulin replacement, we found no reason that BBT should not be standard prenatal care for pregnancies complicated by DM.

Keywords: apidra, aspart, detemir, diabetes, glargine, glulisine, humalog, insulin analogues, insulin type, insulin, intermediate-acting, lantus, levemir, lispro, literature review, long acting insulin analogues, long-acting, novolog, neutral protamine hagedorn, pregnancy, rapid-acting, short acting insulin analogues

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Received: October 17, 2015 | **Published:** November 23, 2015

Abbreviations: DM, diabetes mellitus; NPH, neutral protamine hagedorn; BBT, basal bolus therapy; GDM, gestational diabetes mellitus; LGA, large for gestational age; IUGR, intrauterine growth restriction; T1, trimester; PGDM, pregestational; T2DM, type 2 diabetes mellitus

Introduction

The maternal, fetal and neonatal complications of having diabetes during pregnancy, whether pre-gestational (PGDM) or gestational (GDM), have been well-established in the literature, prompting recommendations that women achieve and maintain strict glycemic control before and during pregnancy.[1] DM-associated maternal complications include progression of retinopathy, nephropathy, hypertension, and preeclampsia. DM-associated fetal and neonatal complications include congenital malformations, stillbirth, macrosomia, shoulder dystocia, intrauterine growth restriction (IUGR).[2,3] Poor glycemic control (glycated hemoglobin (A1c) ≥7%) in the first trimester (T1) is associated with an increased rate of major congenital malformations and spontaneous abortions. In the third trimester (T3), poor glycemic control is associated with increased rate of preterm birth, preeclampsia and perinatal mortality.[2,4] However, simply targeting A1c levels is inadequate to prevent such complications. Insulin requirements vary throughout pregnancy: increasing in early pregnancy (for mean requirement of 0.7units/kg), may decrease in the second half of T1, likely due to nausea and vomiting, then increase in second trimester (T2) (mean 0.8units/kg) and T3 (mean 0.9-1.0units/kg), and lastly, either plateaus or decreases beyond 32 weeks' gestation.[5] Insulin dosing must be continually managed and altered on an individual basis. Therefore, stringent glycemic control during pregnancy strives to minimize glucose excursions throughout the day.[6]

Physiologic pancreatic beta cell secretion of insulin consists of a continuous rate of basal insulin and stimulated bolus insulin, released in response to an exogenous glucose load. Basal insulin secretion regulates lipolysis and hepatic glucose production in between meals.[7] Conventional insulin therapy during pregnancy includes human regular insulin and neutral protamine Hagedorn (NPH); these fail to optimally simulate physiologic insulin release.[8] Through the advent of recombinant DNA techniques, both rapid- and long-acting analogues were used to create products that mimic physiologic insulin profiles.[6]

Without the use of continuous subcutaneous insulin infusion, basal-bolus therapy (BBT), most closely simulates physiologic insulin profiles with the use of a long-acting insulin analogue used as basal insulin, coupled with a rapid-acting analogue given preprandially.[1] It is known that GDM increases a woman's risk of developing future type 2 diabetes mellitus (T2DM).[9] Having patients become familiar with BBT during pregnancy could improve continuity of care for women with PGDM and those with GDM, who may later develop T2DM.

The conventional regular insulin has a 30-minute onset of action (Table 1). This delayed onset of action requires it be administered 30 minutes prior to meals.[8] In clinical practice, however, rapid-acting analogues get substituted for regular insulin in the conventional insulin regimen. Patients administer regular insulin immediately prior to meals and consequently, patients experience postprandial hyperglycemia, followed by hypoglycemia 30 minutes later.[1] Rapid-acting insulin analogues, like insulin aspart, lispro and glulisine are better options for simulating physiologic postprandial insulin action, allowing for more convenient dosing- immediately preprandially. Compared to regular insulin, rapid-acting insulin is associated with lower rates of 1- and 2-hour postprandial hyperglycemia. This may be important for perinatal outcome as postprandial hyperglycemia is more predictive of neonatal complications than is elevated fasting blood glucose levels.[6,7] Rapid-acting analogues also reduce the risk of late postprandial hypoglycemia, helping to minimize daily glucose excursions.[10]

Table 1 Action profiles of different insulin types.[59]

Insulin type		Onset	Peak	Duration
Rapid-Acting	Insulin Lispro (Humalog)	5-15min	30-90min	4-6hr
	Insulin Aspart (NovoLog)	5-15min	30-90min	4-6hr
	Insulin Glulisine (Apidra)	5-15min	30-90min	4-6hr
Short-Acting	Regular Insulin	30-60min	2-3hr	8-10hr
Intermediate-Acting	NPH	2-4hr	4-10hr	12-18hr
	Insulin Detemir (Levemir)	3-4hr	None	20hr
Long-Acting	Insulin Glargine (Lantus)	2-4hr	None	20-24hr

NPH is intermediate-acting insulin used a basal insulin that fails to mimic physiologic insulin secretion. It has a delayed onset of 2-4 hours, peaking in 4-10 hours, and lasting 12-18 hours (Table 1), whereas glargine and detemir successfully create a near peakless action profile.[7,8] Glargine has a duration of action of approximately 24 hours, whereas detemir has a shorter duration of action of 20 hours (Table 1). Clinically, this requires the use of multiple daily doses of NPH that rarely achieve a steady state of basal insulin. Whereas steady state basal insulin is achieved with the use of long-acting insulin analogues. Daily doses of basal insulin detemir requires twice daily dosing, while glargine necessitates once daily dosing.[8] Benefits of long-acting analogues include lower serum fasting glucose levels. Reduced risk of nocturnal hypoglycemia and, less glycemic variability.[10]

BBT using insulin analogues is standard care for non-pregnant individuals affected by T2DM. However, due to the lack of adequately powered randomized clinical trials evaluating the antenatal use of BBT, its routine use during pregnancy is not recommended by most experts. A review of the literature suggests that when compared to the current standard therapy (NPH and regular insulin regimen), BBT with insulin analogues used as therapy for pregnancies complicated by PGDM and GDM during pregnancy, have been associated with improved patient satisfaction and glycemic control.[8,11] We suggest these reported benefits as well as enabling therapeutic continuity for gravidas with PGDM, that insulin analogues become standard of insulin care during pregnancy. The widespread, often inadvertent use of BBT during pregnancy, will likely prevent conduction of an adequately powered randomized trial to compare the perinatal risks and benefits of BBT versus standard perinatal insulin regimen, therefore we conducted a systematic literature review of insulin analogue use during pregnancy to evaluate the evidence concerning BBT use in pregnancy.

Methods

Electronic literature search using PubMed, Medline, Cochrane Library were performed for randomized clinical trials, prospective, retrospective, observational, case reports and case series, using search terms, insulin analogues, lispro, aspart, detemir, glargine, glulisine, Humalog, NovoLog, Lantus, Levemir, Apidra, pregnancy, and diabetes, that were published between 1996 and 2014. Studies included case reports and series, randomized clinical trials, prospective and retrospective observational studies evaluating rapid and long-acting insulin analogues in pregnancies complicated by either PGDM or GDM. Studies assessing efficacy, safety, and historical comparisons between analogues were included. Review articles were excluded. Search was limited to human studies and in the English language. The principal efficacy endpoint examined was glycemic control through A1c levels. Maternal safety outcomes were incidence of hypoglycemic events, fasting and postprandial hyperglycemia Neonatal outcomes included rate of large for gestational age (LGA) or macrosomic (>4000g birth weight) infants, mean birth weight, rate of congenital malformations, and incidence of hypoglycemic events.

Results

Nineteen reports were identified that assessed the use of rapid-acting insulin analogues, lispro and aspart, as hypoglycemic agents during pregnancy. Their prenatal use was associated with significant decreases in A1c, incidence of maternal hypoglycemia, comparable rates of neonatal hypoglycemia and congenital malformations when compared to regular insulin use. Twenty-three reports assessed the safety and efficacy or the long-acting insulin analogues, glargine and detemir. These agents were associated with significant decreases in A1c, maternal and neonatal hypoglycemia with no increase in rates of LGA/macrosomia infants or congenital malformations.

A total of 42 studies were included. Of those, 3 were uncontrolled studies of lispro, 10 were either observational or randomized studies comparing insulin lispro to NPH insulin. Mecacci et al.[12] compared lispro and regular insulin to healthy controls, rather than to each other. Three publications on randomized controlled trials comparing insulin aspart to NPH insulin were included; of these, Mathiesen et al.[13] and Hod et al.[14] reported on the same study. One study compared both rapid-acting insulin analogues (lispro and aspart) to regular insulin. Four uncontrolled observational studies of glargine were included, 7 studies compared glargine use to NPH and one study compared glargine to detemir. Of the 7 studies comparing glargine to NPH, Imbergamo et al.[15] compared glargine users to healthy controls for fetal and neonatal outcomes. Two uncontrolled studies of detemir

were included and 2 publications by Mathiesen et al.[13] and Hod et al.[14] reporting on the same randomized controlled trial comparing detemir to NPH were included.

Rapid-acting insulin analogues

Glulisine: There are no published reports of the use of insulin glulisine in pregnancy.

Lispro: Lispro is the most well-studied insulin analogue used during pregnancy. An early case report by Diamond & Kormas[16] reported possible adverse fetal effects of lispro in 2 diabetic mothers. One pregnancy was terminated and was found to have multiple heart abnormalities, polysplenia, and abdominal situs inversus. The second infant was born at full term and died suddenly at 3 weeks' and was found to have congenital diaphragmatic hernia and bilateral undescended testes.[16]

Three uncontrolled studies evaluated the effects of lispro during pregnancies complicated by PGDM (Table 2) (Table 3). Masson et al.[17] included data from 71 subjects with T1DM and reported decreased A1c from levels in the preconception period to T3 (7.4 ± 1.7 to 6.17 ± 0.85). Early during gestation, the authors reported that 12 women experienced 12 episodes of severe hypoglycemia. In terms of neonatal outcomes, 2 had congenital malformations, 29 neonates had hypoglycemia, and 35% had birth weights of ≥90th percentile for gestational age.[17] Garg et al.[18] studied 62 parturients with T1DM treated with lispro, who had a mean preconception A1c of 7.2 ± 0.2, that decreased to 5.8 ± 0.1 at delivery. Fourteen gravida experienced severe hypoglycemic episodes or 0.61events/patient. Two neonates had congenital malformations and 24% were LGA.[18] A retrospective cohort analysis from Wyatt et al.[19] of 496 women with PGDM treated with lispro found a mean A1c value at the first prenatal visit of 8.9 ± 4.2 to be significantly reduced to 6.2 ± 2.4 in T3 ($p<0.001$). The rates of major congenital abnormalities, LGA infants, and mean birth weight were 5.4% (95% CI [3.45-7.44%]) and 23.4%, and 3464 ± 765g, respectively.[19]

Table 2 Maternal outcomes with lispro use during pregnancy

Authors	Study design	Study population	Number of patients	Mean A1c (%)‡‡	Maternal hypoglycemia (n)	Maternal hypoglycemia (events/patient)	Fasting glucose (mg/dL)	Postprandial glucose (mg/dL)
Diamond[12]	Case Report	PGDM*	2	<7.0	N/A	N/A	<108.0	N/A
Masson[13]	Retrospective	T1DM	71	7.4 ± 1.7 (preconception) 6.17 ± 0.85 (T3)	12	0.65	N/A	N/A
Garg[14]	Retrospective	T1DM	62	7.2 ± 0.2 (preconception) 5.8 ± 0.1 (intrapartum)	14	0.61	N/A	N/A
Wyatt[15]	Retrospective	T1DM, T2DM	496	8.9 ± 4.2 (first prenatal visit) 6.2 ± 2.4 (T3)	6.9% (T1), 6.6% (T2), 2.4% (T3)	N/A	N/A	N/A
Jovanovic[16]	RCT	GDM	19 Lispro	5.16 ± 0.09	N/A	N/A	79.8 ± 2.9	86.8 ± 4.6†
			23 Regular	5.12 ± 0.09	N/A	N/A	81.5 ± 2.8	99.6 ± 4.7† p=0.025
Buchbinder[17]	Retrospective	T1DM	12 Lispro	No difference	N/A	N/A	N/A	N/A
			42 Regular		N/A	N/A	N/A	N/A
Bhattacharyya[18]	Retrospective	T1DM, T2DM, GDM	89 Lispro	5.8 ± 0.40 (GDM) 6.80 ± 0.61 (PGDM)	N/A	N/A	N/A	N/A
			131 Regular	6.08 ± 0.68 (GDM) 6.86 ± 0.40 (PGDM) p<0.05	N/A	N/A	N/A	N/A

Table Continues...

Authors	Study design	Study population	Number of patients	Mean A1c (%)‡‡	Maternal hypoglycemia (n)	Maternal hypoglycemia (events/patient)	Fasting glucose (mg/dL)	Postprandial glucose (mg/dL)
Persson‡[23]	RCT	T1DM	16 Lispro	5.2 (4.6-5.9) (before delivery)	0	N/A	116.64±45.18**	Significantly lower in lispro group after breakfast (p<0.01)
			17 Regular	5.0 (4.5-6.7) (before delivery)	2	N/A	128.88±53.64**	
Loukovaara[19]	RCT	T1DM	36 Lispro	No difference in T1	8	N/A	N/A	N/A
			33 Regular	Significantly lower in Lispro group in T2 and T3 (p=0.022)	11	N/A	N/A	N/A
Mecacci††[24]	RCT	GDM	25 Lispro	N/A	N/A	N/A	Significantly higher than healthy controls	Similar to healthy controls
			24 Regular	N/A	N/A	N/A	Significantly higher than healthy controls	Significantly higher than healthy controls
Cypryk[20]	Prospective	T1DM	25 Lispro	7.8±1.4	N/A	N/A	N/A	N/A
			46 Regular	7.5±1.5	N/A	N/A	N/A	N/A
Lapolla[55]	Retrospective	T1DM	72 Lispro	6.7±1.4	2.80%	N/A	N/A	N/A
			298 Regular	7.3±1.4 p<0.001	5.40%	N/A	N/A	N/A
Aydin[21]	Retrospective	PGDM*, GDM	27 Lispro	6.27±2.23	N/A	N/A	N/A	N/A
			59 Regular	7.07±2.09	N/A	N/A	N/A	N/A
Durnwald[26]	Prospective	T1DM, T2DM	58 Lispro	5.9±1.0 (T2, T3)	N/A	N/A	N/A	N/A
			49 Regular	6.7±1.3 (T2, T3) p=0.009	N/A	N/A	N/A	N/A
Garcia-Dominquez[27]	Retrospective	T1DM, T2DM	110 Lispro	6.9±1.1	2.30%	N/A	N/A	N/A
			241 Regular	6.6±1.0 p=0.022	10.00% p=0.025	N/A	N/A	N/A
Di Cianni[28]	Retrospective	GDM	18 Lispro	No difference	0	N/A	No difference	118.8±18.9**
			23 Regular		0	N/A		135±23.4** p<0.05

Values statistically significant would be indicated with p-value

‡‡Unless otherwise specified, A1c is mean or T1 level.

†2 hour postprandial measurement

‡Patients randomized at 14 weeks' gestation

*Authors did not specify T1DM vs T2DM for PGDM

**Results converted from reported mmol/L to mg/dL

††Authors compared Lispro and Regular to healthy controls

Table 3 Neonatal outcomes with Lispro use during pregnancy

Authors	Study population	Number of patients	LGA/macrosomia, n (%)	Birth weight (g)	Congenital malformations, n (%)	Neonatal hypoglycemia, n (%)
Diamond[12]	PGDM*	2	N/A	N/A	2 (100.0)	N/A
Masson[13]	T1DM	71	25 (35)	3230	2 (4.2)	29 (40.8)
Garg[14]	T1DM	62	14 (24)	3400±100	2 (3.2)	N/A
Wyatt[15]	T1DM, T2DM	496	117 (23.4)	3463±765	27 (5.4)	N/A

Table Continues...

Authors	Study population	Number of patients	LGA/macrosomia, n (%)	Birth weight (g)	Congenital malformations, n (%)	Neonatal hypoglycemia, n (%)
Jovanovic[16]	GDM	19 Lispro	0 (0)	3098±202	N/A	0 (0)
		23 Regular	0 (0)	3169±78	N/A	0 (0)
Buchbinder[17]	T1DM	12 Lispro	N/A	N/A	N/A	N/A
		42 Regular	N/A	N/A	N/A	N/A
Bhattacharyya[18]	T1DM, T2DM, GDM	89 Lispro	N/A	3290±570 (GDM)	1 (1.3) GDM	17% (GDM)
				3270±104 (PGDM)	0 (0) PGDM	20% (PGDM)
		131 Regular	N/A	3260±810 (PGDM)	3 (2.2) GDM	30% (GDM)
				3310±580 (GDM)	4 (7.0) PGDM	19% (PGDM)
Persson‡[23]	T1DM	16 Lispro	No difference	No difference	0 (0)	N/A
		17 Regular			1 (5.88)	N/A
Loukovaara[19]	T1DM	36 Lispro	N/A	N/A	N/A	N/A
		33 Regular	N/A	N/A	N/A	N/A
Mecacci††[24]	GDM	25 Lispro	No difference	3321±247	N/A	N/A
		24 Regular		3271±389	N/A	N/A
Cypryk[20]	T1DM	25 Lispro	10 (43.5)	3467±790	0 (0)	4 (17.4)
		46 Regular	13 (30.3)	3367±666	1 (2.17)	10 (23.3)
Lapolla[55]	T1DM	72 Lispro	14.50%	3404±611	3 (4.3)	N/A
		298 Regular	11.50%	3288±662	14 (4.5)	N/A
Aydin[21]	PGDM*, GDM	27 Lispro	7.40%	3203±0.802	0 (0)	N/A
		59 Regular	13.60%	3168±0.741	9 (15.25)	N/A
Durnwald[26]	T1DM, T2DM	58 Lispro	32.80%	3569±526	2 (3.45)	41.40%
		49 Regular	20.40%	3246±764 p=0.01	2 (4.08)	38.80%
Garcia-Dominquez[27]	T1DM, T2DM	110 Lispro	N/A	N/A	3.30%	34.9% (on insulin pump)
		241 Regular	N/A	N/A	3.60%	23.60% p=0.043
Di Cianni[28]	GDM	18 Lispro	12.10%	Significantly greater with Regular Insulin group (p<0.04)	N/A	N/A
		23 Regular	15.60%		N/A	N/A

Values statistically significant would be indicated with p-value

‡Patients randomized at 14 weeks' gestation

*Authors did not specify T1DM vs T2DM for PGDM

††Authors compared Lispro and Regular to healthy controls

Twelve studies (4 randomized trials and 8 observational studies) comparing both maternal and neonatal outcomes in PGDM and GDM treated with lispro versus human insulin are reported in Tables 2 & 3. Jovanovic et al.[20] randomized 42 women diagnosed with GDM between 14 and 32 weeks' of gestation, who were insulin naïve, to lispro (19 women) and regular insulin (23 women). A test meal consisting of 20% of daily caloric need was given before breakfast and followed by subcutaneous injection of the calculated initial daily insulin of either lispro or regular insulin. Scheduled measurement of glucose concentrations were fasting, 60 min, 120 min, and 180 min following the meal. The authors reported significantly lesser area under the curve for lispro (p=0.025). However, A1c measured 6 weeks later showed no significant differences between groups (p=0.7508). The group treated with lispro experienced fewer pre-breakfast hypoglycemic events (<55mg/dL), but not before lunch or dinner.

Mean birth weight, frequency of macrosomia, intrauterine growth restriction (IUGR), and fetal abnormalities did not significantly differ.[20]

Buchbinder et al.[21] retrospectively analyzed patients with T1DM treated with lispro (n=12) and regular insulin (n=42). Overall, there were no statistically significant differences in glycemic control between the 2 groups during pregnancy and postpartum.[21] Similarly, Bhattacharyya et al.[22] conducted a retrospective cohort study of PGDM and GDM patients and demonstrated no differences in fetal outcomes. However, pre-delivery A1c levels in the lispro group were significantly lower than regular insulin and diet-controlled groups (p<0.05). In addition, patient satisfaction was significantly higher in the lispro group compared to regular insulin (26.3±2.3 vs. 18±8.9, p=0.0005).[22]

Loukovaara et al.[23] conducted a randomized trial on women with T1DM (lispro, n=36 and regular insulin, n=33). They found lower, but non-significant, rates of maternal hypoglycemia (9 vs. 11 women, p=0.42) throughout pregnancy. A1c levels were significantly lower in the lispro group in T2 and T3, but not in T1 (p=0.022).[23]

No significant difference was demonstrated in A1c levels in any trimester in a prospective observational and retrospective observational study by Cypryk et al.[24] & Aydin et al.[25] respectively. By contrast, Lapolla et al.[26] reported a significantly lower A1c level in T1 in the lispro versus regular group (6.7±1.4 vs. 7.3±1.4, p<0.001), but no difference in A1c in T3 (6.0±1.0 lispro vs. 6.2±1.2 regular).[26] Rates of maternal hypoglycemia were lower but non-significant in the lispro group (2.8% vs. 5.4%). Incidences of congenital malformations were similar (4.3% vs. 4.5%). However, incidence of LGA was significantly higher in the lispro group (55.1% vs. 39.2%, p=0.0267). Cypryk et al.[24] demonstrated a non-significant decrease in the rate of neonatal hypoglycemia (17.4% in lispro group vs. 23.3% in regular insulin group). There were no reports of congenital malformations in either study.

In 2002, randomized controlled trial conducted by Persson et al.[27] randomized 16 women to lispro and 17 to regular insulin at 14 weeks' gestational age. Postprandial breakfast glycemic control significantly improved in the lispro compared to regular insulin group (p<0.01). Only one congenital malformation with regular insulin was reported. Although there was an associated increase in rate of maternal biochemical hypoglycemic events (<54mg/dL) in those treated with insulin lispro (5.5 vs. 3.9%, p<0.05), only the regular insulin group experienced severe hypoglycemia episodes.[27]

Mecacci et al.[12] enrolled 25 patients on lispro and 24 on regular insulin in a randomized trial of women with GDM, and compared them to 50 healthy controls. The 1-hour postprandial blood glucose concentrations were significantly higher in the regular insulin group, but similar for the 2 study groups at 2-hours. The rate of neonates born with a cranio-thoracic circumference ratio between the 10th and 25th percentile was significantly higher in the regular insulin group. The authors found no differences in neonatal outcomes between treatment groups.[12]

In 2005, Plank et al.[28] found no significant differences in fetal or maternal outcome between pregnant patients using insulin lispro and aspart.[28] A prospective observational study by Durwnald et al.[29] demonstrated significantly improved A1c over T2 and T3 in those treated with insulin lispro versus regular insulin (5.9±1.0 vs 6.7±1.3, p=0.009). In addition, while the mean birth weight was significantly higher in the lispro group (3569±526g vs. 3246±764g, p=0.01), the incidence of LGA (32.8% vs. 20.4%, p=0.15) and neonatal hypoglycemia (41.4% vs. 38.8%) in the study groups were not statistically significant. Congenital malformation was identified in one patient exposed to lispro and two in the regular insulin group.[29]

In 2011, Garcia-Dominque et al.[30] retrospectively evaluated 241 parturients treated with regular insulin and NPH and 110 with various combinations of insulin analogues (most commonly, a combination of lispro and NPH).[30] The group treated with insulin analogues had slightly higher mean A1c during T1 (6.9±1.0 vs. 6.6±1.0, p=0.022), but required smaller insulin doses throughout pregnancy. The frequency of severe hypoglycemia was significantly less among rapid-acting analogue users (2.3 vs. 10.0%, p=0.025).The treatment groups had similar rates of congenital malformations. In contrast, neonatal hypoglycemia was significantly more frequent in the rapid-acting

analogue group (34.9 vs. 23.6%, p=0.043), but the authors attributed this to the concomitant use of an insulin pump.

Di Cianni et al.[31] conducted a smaller clinical trial of women with GDM who were randomized to receive lispro, aspart or regular insulin with NPH as basal insulin.[31] The groups were matched for age, parity, BMI, gestational age and weight gain. One-hour postprandial glucose levels after breakfast were significantly higher in the regular insulin group when compared to the lispro and aspart groups (135±23.4, 118.8±18.9, 121.5±20.16mg/dL, respectively, ANOVA p<0.05). Birth weight was higher in the regular insulin group (p<0.04) and similarly, LGA rates were 15.6%, 12.1%, and 9.6% in regular insulin, lispro, and aspart groups, respectively.

To date, there are two published papers who performed a meta-analysis comparing lispro to regular insulin. One article by Gonzalez Blanco et al.[32] looking at only T1DM, included four studies into their analysis revealed no differences in maternal or neonatal outcomes with the exception of a higher rate of LGA newborns (RR 1.38[1.14-1.68]).[32] A larger and more recent meta-analysis by Lv et al.[33] assessed the safety of four insulin analogs: lispro, aspart, glargine, and determir. Twenty-four studies met their inclusion criteria which involved both pre-gestational and gestational diabetic pregnant patients. They reported no significant difference in the maternal and neonatal outcomes in patients using aspart, glargine, and determir. However, insulin lispro was associated with higher birth weight and an increased rate of LGA newborns, similar to the findings of the previous meta-anaylsis.[33]

Aspart: Aspart use in pregnancy has not been as well studied as has been with lispro. We have included four studies that evaluate the use of aspart in pregnancy (Table 4) (Table 5).

The first published study was authored by Pettitt et al.[34] in 2003 (Table 4). Twenty-seven women with GDM were enrolled in a prospective cross-over trial. Area under the curve of glucose concentrations from the preprandial period to 240 minutes after a test meal consisting of 20% of daily caloric needs was measured. Either aspart or regular insulin was given the first day, which was followed by administration of the other insulin the next day. The area under the curve was significantly lower with aspart (p=0.018) but not with regular insulin (p=0.997), compared to no insulin use. One congenital malformation was reported in the aspart group. The authors reported no macrosomic infant in either group.[34]

A large open-label, randomized, parallel-group trial by Mathiesen et al.[13] and Hod et al.[14] investigated 322 women with T1DM, who had been treated with insulin for more than 12 months and had preconception A1C <8%.[13,14] Subjects were randomized to aspart or regular insulin, coupled with NPH used as basal insulin. The primary study endpoint was major maternal hypoglycemia (requiring assistance with <55.8mg/dL or reversal of symptoms after food, glucagon, or intravenous glucose); this was not significantly lower in the group treated with aspart (RR 0.720 [95% CI 0.36–1.46]). Both groups showed decreased A1c during T1 and T2, followed by an increase at delivery and at 6 weeks' postpartum. No statistical significance in glycemic control was reported in T2 and T3. The incidence of congenital malformations was 4.3% and 6.6% for aspart and regular insulin, respectively. There were no significant differences between treatment arms in birth weight and rates of neonatal hypoglycemia requiring treatment (33.6% aspart vs. 39.7% regular insulin). In addition, the aspart treatment group had greater overall treatment satisfaction due to increased flexibility in treatment and is

demonstrated by their willingness to continue on the study regimen after delivery.

Heller et al.[35] published a randomized, multicenter trial of 322 women affected by T1DM in 2010; 99 of these patients were randomized pre-pregnancy and 223 randomized early during the pregnancy, to either aspart or regular insulin for bolus therapy, in combination with NPH for basal therapy. They found no differences in A1c levels between treatment groups, but also demonstrated fewer, but not statistically significant, maternal hypoglycemic episodes with aspart use versus regular insulin (0.9 vs. 2.4 events per patient per year in the first half of pregnancy, and 0.3 vs. 1.2 events per patient per year in the second half of pregnancy).[35]

See above Lispro section for results from Di Cianni et al.[31]

Table 4 Maternal outcomes with aspart use during pregnancy

Authors	Study design	Study population	Number of patients	Mean A1c (%)‡‡	Maternal hypoglycemia (n)	Maternal hypoglycemia (events/patient)	Fasting glucose (mg/dL)	Postprandial glucose (mg/dL)
Heller[34]	RCT	T1DM	157 Aspart	6.3±0.7‡ 6.3±0.6‡‡	N/A	0.9 (preconception)† 0.9 (first half pregnancy)† 0.3 (second half pregnancy)† 0.2 (postpartum)†	N/A	N/A
			165 Regular	6.2±0.7‡ 6.4±0.7‡‡	N/A	2.4 (preconception)† 2.4 (first half pregnancy)† 1.2 (second half pregnancy)† 2.2 (postpartum)†	N/A	N/A
Mathiesen/ Hod*[32,33]	RCT	T1DM	157 Aspart	No difference	38	1.4†	No difference	Aspart group significantly lower than Regular (T1 p=0.003, T3 p=0.044)
			165 Regular		35	2.1†		
Di Cianni[28]	RCT	GDM	16 Aspart	No difference	0	N/A	No difference	121.5±20.16**
			23 Regular		0	N/A		135±23.4** p<0.05
Pettitt[29]	RCT	GDM	13 Aspart	N/A	N/A	N/A		Area under curve from pre-prandial to 4 hr post-prandial significantly lower with aspart (p=0.018) but not Regular (p=0.997).
			14 Regular	N/A	N/A	N/A		

Values statistically significant would be indicated with p-value

‡‡Unless otherwise specified, A1c is mean or T1 level.

*Authors reported on same study

**Results converted from reported mmol/L to mg/dL

†Rate in number of hypoglycemic episodes/year of exposure

‡Randomly assigned preconception

‡‡Randomly assigned in early pregnancy

Table 5 Neonatal outcomes with aspart use during pregnancy

Authors	Study population	Number of patients	LGA/ macrosomia, n (%)	Birth weight (g)	Congenital malformations, n (%)	Neonatal hypoglycemia, n (%)
Heller[34]	T1DM	157 Aspart	N/A	N/A	N/A	N/A
		110 Regular	N/A	N/A	N/A	N/A
Mathiesen/Hod*[32,33]	T1DM	157 Aspart	N/A	3438±71.5	6 (4.3)	46 (33.6)
		165 Regular	N/A	3555±72.9	9 (6.6)	52 (39.7)
Di Cianni[28]	GDM	16 Aspart	9.60%	Significantly greater with Regular Insulin (p<0.04)	N/A	N/A
		23 Regular	15.60%		N/A	N/A

Table Continues...

Authors	Study population	Number of patients	LGA/ macrosomia, n (%)	Birth weight (g)	Congenital malformations, n (%)	Neonatal hypoglycemia, n (%)
Pettitt[29]	GDM	13 Aspart	N/A	3100±500	1 (7.7)	N/A
		14 Regular	N/A	3000±500	0	N/A

Values statistically significant would be indicated with p-value

*Authors reported on same study

Long acting insulin analogues

Glargine: To date, there are no randomized trials studying the safety and efficacy of glargine use during pregnancy. However, glargine is the long-acting insulin analogue that has been well studied through case reports and observational studies (Table 6) (Table 7).

The first reports of glargine use in pregnancy stem from a set of case reports published between 2002 and 2007. Few pregnant patients were switched from NPH to glargine due to recurrent hypoglycemic episodes. Others had either willingly continued using glargine despite the unknown effects or were not aware of their pregnancy until 6-12 weeks' gestation. No congenital malformations were reported, although two infants were LGA.[36–42]

Table 6 Maternal outcomes with Glargine use during pregnancy

Authors	Study design	Study population	Number of patients	Mean A1c (%)‡‡	Maternal hypoglycemia, n (%)	Maternal hypoglycemia (events/patient)	Fasting glucose (mg/dL)	Postprandial glucose (mg/dL)
Devlin[35]	Case Report	T1DM	1	<6.0	N/A	N/A	N/A	N/A
Woolderink[40]	Retrospective	T1DM	7	6.4	N/A	N/A	N/A	N/A
Di Cianni[36]	Case Series	T1DM	5	6.0±0.2	N/A	N/A	N/A	N/A
Dolci[37]	Case Report	T1DM	1	6.2	N/A	N/A	N/A	N/A
Graves[37]	Case Series	T1DM	4	N/A	1 (25)	N/A	N/A	N/A
Caronna[41]	Case Report	T1DM	1	N/A	N/A	N/A	N/A	N/A
Torlone[39]	Case Series	T1DM	6	6.1±0.2	N/A	N/A	N/A	N/A
Gallen[42]	Prospective	T1DM	114	8.1±1.7 (at booking) 6.8±0.1 (T3)	25 (22)	N/A	N/A	N/A
Di Cianni◊[45]	Retrospective	T1DM	43 Glargine	7.7±1.32 (first prenatal visit) 6.5±0.79 (end of pregnancy)	9.30%	N/A	N/A	N/A
			58 NPH	7.6±1.09 (first prenatal visit) 6.5±0.91 (end of pregnancy)	12.10%	N/A	N/A	N/A

Table Continues...

Authors	Study design	Study population	Number of patients	Mean A1c (%)‡‡	Maternal hypoglycemia, n (%)	Maternal hypoglycemia (events/patient)	Fasting glucose (mg/dL)	Postprandial glucose (mg/dL)
								N/A
Lepercq[43]	Retrospective	T1DM	102	6.7±1.2 (T1) 6.20±0.9 (T3)	N/A	N/A	N/A	
Henderson[44]		T2DM, GDM	240	N/A	N/A	N/A	112±14.8‡	-
Price[46]	Case-control	T1DM, GDM	32 Glargine	6.9±0.89 (T1DM) 6.2±0.85 (GDM)	No difference	N/A	115.2±12.4 (T1DM)‡ 109.8±18.0 (GDM)‡	-
			32 NPH	6.7±0.69 (T1DM) 6.1±0.60 (GDM)		N/A	115.2±11.9 (T1DM)‡ 118.8±16.7 (GDM)‡	-
Poyhonen-Alho[47]	Case-control	T1DM	42 Glargine	7.6±0.2	4 (9.5)	N/A	N/A	N/A
			49 NPH	7.2±0.3	2 (4.1)	N/A	N/A	N/A
Imbergamo††[48]	Retrospective	T1DM	15 Glargine	6.86±0.95	1 (6.7)	N/A	135.7±39.6 (T1) 122.9±25.4 (T2) 126.9±27.9 (T3)	102.2±31.5 (T1) 102.2±26.8 (T2) 107.6±21.4 (T3)**
			15 NPH	7.79±1.13 p=0.037	0 (0)	N/A	200.5±72 (T1), p=0.008 165.1±50.4 (T2), p=0.015 143.3±40.0 (T3)	158.4±41.2 (T1) p<0.001 126.4±26.1 (T2) p=0.015 124.4±31.9 (T3)**
Smith[49]	Retrospective	T1DM, T2DM, GDM	27 Glargine 25 NPH	No difference	N/A N/A	N/A N/A	No difference	No difference
Fang[50]	Retrospective	PGDM*, GDM	52 Glargine	6.55 (T3)	1 (2.7) (PGDM) 0 (0) (GDM)	N/A	N/A	N/A
			60 NPH	6.7 (T3)	0 (0) (PGDM) 0 (0) (GDM)	N/A	N/A	N/A
Egerman[51]	Retrospective	PGDM*, GDM	65 Glargine	7.04±1.4 (T3)	N/A	N/A	N/A	N/A
			49 NPH	7.48±2.09 (T3)	N/A	N/A	N/A	N/A

Table Continues...

Authors	Study design	Study population	Number of patients	Mean A1c (%)‡‡	Maternal hypoglycemia, n (%)	Maternal hypoglycemia (events/patient)	Fasting glucose (mg/dL)	Postprandial glucose (mg/dL)
Negrato[52]	Prospective	PGDM*, GDM	56 Glargine	7.2±1.3 (PGDM) (36 wks)	0 (0) (PGDM)	N/A	107.9±27.4 (PGDM)	N/A
				6.1±0.8 (GDM)	0 (GDM)		82.8±14.5, p=0.03 vs. NPH (GDM)	N/A
			82 NPH	7.6±2.0 (PGDM) (36 wks)	10 (26.3) (PGDM), p<0.0001	N/A	109.5±37.1 (PGDM)	
				6.1±0.8 (GDM)	1 (2.2) (GDM)		91.6±21.5 (GDM)	N/A
Callesen[53]	Retrospective	T1DM	46 Glargine	6.8 (5.4-10.1) (8 wks)†	10 (23)	N/A	N/A	
				6.2 (4.8-7.2) (33 wks)†				N/A
			67 Detemir	6.6 (5.6-9.8) (8 wks)†	15 (23)	N/A	N/A	
				6.1 (5.1-7.6) (33 wks)†				

Values statistically significant would be indicated with p-value

‡‡Unless otherwise specified, A1c is mean or T1 level

◊Authors compared women who continued glargine throughout pregnancy to women who used glargine early in pregnancy and switched to NPH

‡Overall mean glucose levels

*Authors did not specify T1DM vs T2DM for PGDM

**2 hours post-breakfast glucose; post-lunch and post-dinner values were not significantly different

†Values reported as median values (range)

††Authors compared glargine users to healthy controls for fetal and neonatal outcomes. Patient population used BBT with lispro/aspart with glargine/NPH.

Table 7 Neonatal outcomes with Glargine use during pregnancy

Authors	Study population	Number of patients	Macrosomia, n (%)	Birth weight (g)	Congenital malformations, n (%)	Neonatal hypoglycemia, n (%)
Devlin[35]	T1DM	1	0 (0)	3512	0 (0)	1 (100.0)
Woolderink[40]	T1DM	7	N/A	4180	0 (0)	0 (0)
Di Cianni[36]	T1DM	5	1 (20)	3066±898	0 (0)	N/A
Dolci[37]	T1DM	1	0 (0)	2150	0 (0)	N/A
Graves[37]	T1DM	4	1 (25)	N/A	0 (0)	0 (0)
Caronna[41]	T1DM	1	0 (0)	3540	0 (0)	N/A
Torlone[39]	T1DM	6	1 (16.7)	3160±270	0 (0)	N/A
Gallen[42]	T1DM	114	N/A	3500±600	3 (2.8)	50 (47)
Di Cianni◊[45]	T1DM	43 Glargine	44.10%	N/A	4.70%	14.60%
		58 NPH	41.30%	N/A	5.20%	17.20%
Lepercq[43]	T1DM	102	31 (30)	3381±595	2 (2.0)	N/A
Henderson[44]	T2DM, GDM	240	4 (1.67)	3142±606	N/A	0 (0)
Price[46]	T1DM, GDM	32 Glargine	4 (40.0) (T1DM)	3443±782 (T1DM)	No difference	6 (60.0) (T1DM)
			8 (36.3) (GDM)	3537±520 (GDM)		6 (27.3) (GDM)
		32 NPH	3 (30.0) (T1DM)	3325±356 (T1DM)		6 (60.0) (T1DM)
			10 (45.5) (GDM)	3593±429 (GDM)		3 (13.6) (GDM)

Table Continues...

Authors	Study population	Number of patients	Macrosomia, n (%)	Birth weight (g)	Congenital malformations, n (%)	Neonatal hypoglycemia, n (%)
Poyhonen-Alho[47]	T1DM	42 Glargine	N/A	3796±101	1 (2.4)	12 (28.6)
		49 NPH	N/A	3789±68	0 (0)	17 (34.7)
Imbergamo††[48]	T1DM	15 Glargine	7 (46.7)	3278±786	0 (0)	4 (26.7)
		15 NPH	4 (26.7)	3503±455	0 (0)	1 (6.7)
Smith[49]	T1DM, T2DM, GDM	27 Glargine	6 (22.2)	3294±189	N/A	No difference
		25 NPH	3 (12.0)	3274±189	N/A	
Fang[50]	PGDM*, GDM	52 Glargine	7 (18.92) (PGDM)	3307±517 (PGDM)	0 (0)	0 (0) (PGDM)
			3 (20) (GDM)	3501±473 (GDM)		1 (6.7) (GDM)
		60 NPH	8 (50) (PGDM), p=0.04	3298±885 (PGDM)	0 (0)	4 (25) (PGDM), p=0.01
			7 (15.91) (GDM)	3296±525 (GDM)		2 (4.6) (GDM)
Egerman[51]	PGDM*, GDM	65 Glargine	N/A	3415±1231	10 (15.4)	19 (29.2)
		49 NPH	N/A	3351±1083	8 (16.3)	12 (24.4)
Negrato[52]	PGDM*, GDM	56 Glargine	9 (50.0) (PGDM)	3510±520 (PGDM)	2 (11.1) (PGDM)	2 (11.1) (PGDM)
			13 (35.1) (GDM)	3450±640 (GDM)	1 (1.82) (GDM)	1 (2.7) (GDM)
		82 NPH	14 (36.8) (PGDM)	3290±700 (PGDM)	6 (15.8) (PGDM)	6 (33.3) (PGDM)
			18 (40.0) (GDM)	3300±520 (GDM)	6 (7.23) (GDM)	2 (44.4) (GDM)
Callesen[53]	T1DM	46 Glargine	14 (30.4) p=0.046	3219 (1829-4356)†	1 (2.2)	19 (41.3)
		67 Detemir	33 (49.2)	3490 (1484-4500)† p=0.05	1 (1.5)	25 (37.3)

Values statistically significant would be indicated with p-value

◊Authors compared women who continued glargine throughout pregnancy to women who used glargine early in pregnancy and switched to NPH

*Authors did not specify T1DM vs T2DM for PGDM

†Values reported as median values (range)

††Authors compared glargine users to healthy controls for fetal and neonatal outcomes. Patient population used BBT with lispro/aspart with glargine/NPH.

In 2008, Gallen et al.[43] published an uncontrolled prospective audit of 115 pregnant women with T1DM treated with glargine. Of these, 69% were treated with glargine during the preconception period. Lispro was the bolus insulin in 42%, aspart in 45%, and regular insulin in 8%. Glycemic control assessed by changes in A1c levels improved from enrollment (8.1±1.7) to T3 (6.8±0.1). Severe maternal hypoglycemia, defined as requiring third-party assistance, was reported in 22%. In terms of neonatal outcomes, 47% (50/114) of neonates experienced hypoglycemia, mean birth weight was 3500±600g, and three had congenital abnormalities.[43]

Similarly, Lepercq et al.[44] studied 102 women with T1DM treated with glargine and demonstrated improvement in mean A1C from T1 to T3 (6.7±1.2 to 6.2±0.9). Two congenital malformations were noted and LGA rate was 30%.[44] Henderson et al.[45] conducted a retrospective review of 240 women with T2DM and GDM and found a mean glucose level of 112±14.8mg/dL, birth weight of 3142±606g and 4 macrosomic infants.[45]

Di Cianni et al.[46] retrospectively observed a cohort of 107 women who used glargine for at least one month preconception and during pregnancy. Six pregnancies ended with abortion, 4 of which were spontaneous. The comparison groups were 43 women who had continued with glargine throughout pregnancy and 58 women who started using glargine in early pregnancy and switched to NPH, based on individual center policies. All patients showed improvement in glycemic control during pregnancy measured as A1c, from 7.7±1.32 at first prenatal visit to 6.5±0.79 at end of pregnancy in glargine group and 7.6±1.09 to 6.5±0.91 in NPH group. Maternal hypoglycemia was reported in 9.3% and 12.1% in glargine and NPH groups, respectively. The rates of LGA, macrosomia, congenital malformations and neonatal hypoglycemia were comparable between groups.[46]

Price et al.[47] conducted a case-control study in women with T1DM and GDM. Thirty-two women previously treated with glargine were selected (10 T1DM, 22 GDM) using either lispro or aspart for bolus therapy. Cases were matched for type and duration of diabetes, duration of insulin therapy during pregnancy, parity, maternal height, and weight at first prenatal visit, gestational age at delivery, fetal sex, and glycemic control. Third trimester glycemic control and incidence of daytime and nocturnal hypoglycemia were not significantly different between groups. Birth weight and rate of congenital abnormalities were similar. Overall incidence of macrosomia was similar: 37.5% in glargine group and 40.6% in control group (p>0.05).[47]

Poyhonen-Alho et al.[48] conducted a case-control study of women with T1DM. Forty-two received glargine, while 49 were treated with NPH. The glargine group demonstrated a significantly greater

decrease in A1c from T1 to T3 (0.8±0.1) versus NPH (0.3±0.2) (p=0.04). Maternal hypoglycemia rates and birth weight did not differ.[48] Similarly, rates of mild and severe hypoglycemia did not differ either between glargine and NPH in a smaller study from Imbergamo et al.[15] Glargine group had significantly improved fasting and 2-hour post-breakfast glucose levels during T1 and T2. However, the incidence of LGA was 46.7% and 27.6% in the glargine and NPH groups, respectively. No differences in maternal or neonatal outcomes were found in a retrospective analysis by Smith et al.[49]

Fang et al.[50] studied 112 PGDM and GDM women; they compared glargine and NPH use in 2 different patient populations: PGDM and GDM patients. Regular insulin or lispro was used as the prandial insulin regimen. They found no significant differences in the rates of maternal hypoglycemia, T3 A1c levels, and mean birth weight. No congenital abnormalities were noted. In PGDM treated with glargine, 18.9% had LGA infants versus 50% in NPH group (RR 0.38, 95% CI [0.17–0.87], p=0.04). There was only one case of maternal hypoglycemia in the PGDM group treated with glargine. There were no cases of neonatal hypoglycemia in PGDM glargine group, while 25% of the neonates exposed to in utero to NPH (p=0.01) experienced neonatal hypoglycemia. Subgroup analysis found no differences in rates of LGA or of neonatal hypoglycemia in GDM groups between insulin glargine and NPH use.[50]

Egerman et al.[51] evaluated outcomes for 114 women with PGDM and GDM women treated with NPH and insulin glargine. The only significant differences in maternal and neonatal outcomes was an increased incidence of shoulder dystocia in the NPH group (p=0.03).[51] A recent study published in 2010, was a prospective cohort study of 138 women with either PGDM or GDM; PGDM and GDM groups were analyzed separately. Maternal hypoglycemia rates were increased in NPH versus glargine. The PGDM group treated with glargine experienced no hypoglycemic episodes, while 23% of the NPH group experienced hypoglycemia (p<0.0001). The neonatal outcomes for the study groups were not different.[52]

Callesen et al.[53] retrospectively observed 113 women with T1DM and compared 2 basal insulin analogues, glargine and detemir Median A1c levels at 8 weeks' and 33 weeks' for the 2 study groups were comparable. In both groups, 23% experienced at least one occurrence of severe hypoglycemia. Lower mean birth weight (p=0.05) and incidence of LGA infants (p=0.046) were demonstrated in the glargine group.[53]

One meta-analysis of maternal and neonatal outcomes comparing the use of glargine vs NPH insulin incorporating eight studies was conducted by Lepercq et al.[54] in 2012. They reported no significant increased risk of any neonatal or maternal outcomes. They also found no difference in the glycemic control as measured by first and third trimester A1c between insulin glargine and NPH insulin.[54]

Detemir: Detemir is a long-acting insulin analogue that is not as well studied as glargine. The first published report of detemir use in pregnancy was a study of 10 women with T1DM who were treated with detemir for a minimum of 3 months preconception. One patient experienced maternal hypoglycemia, 2 infants were LGA, one experienced neonatal hypoglycemia, and none had congenital malformations. Improved A1c was documented from the beginning of pregnancy (8.1±1.9) to the end (5.9±0.7) (no p-value reported).[55]

A retrospective case series of 18 women with T1DM and T2DM was published by Shenoy et al.[56] (Table 5a & 5b). The authorsreported only one event of severe maternal hypoglycemia. Half of the infants were LGA, and 13 of 18 infants experienced neonatal hypoglycemia. Maternal glycemic control improved from preconception (8.6%) to T3 (7.0%).[56]

A large open-label, randomized, parallel-group study of women with T1DM had results published by Mathieson et al.[57] & Hod et al.,[58] (Table 8) (Table 9). Patients were randomized to detemir (n=152) or NPH (n=158) up to 12 months preconception or at 8-12 weeks' gestational age and continued until 6 weeks postpartum. Inclusion criteria include A1c <8% at confirmation of pregnancy. Insulin aspart was used as the bolus insulin. The primary endpoint was A1c at 36 weeks' gestation and secondary endpoints included fasting glucose, major and minor hypoglycemia, and adverse events. The mean A1c at 36 weeks' was 6.27% and 6.33% for detemir and NPH groups, respectively (difference -0.06 [95% CI -0.21 to 0.08]). Mean fasting glucose was significantly lower in detemir group at 24 (p=0.012) and 36 weeks' gestation (p=0.017). Major hypoglycemia events were not significantly different (16% in detemir group, 21% in NPH group).

See Glargine section above for results of Callesen et al.[53]

Table 8 Maternal outcomes with Detemir use during pregnancy

Authors	Study design	Study population	Number of patients	Mean A1c (%)‡‡	Maternal hypoglycemia, n (%)	Maternal hypoglycemia (events/patient)	Fasting glucose (mg/dL)	Postprandial glucose (mg/dL)
Lapolla[55]	Retrospective	T1DM	10	8.1±1.9 (first prenatal visit) 5.9±0.7 (end of pregnancy)	1 (10.0)	N/A	N/A	N/A
Shenoy[56]	Case Series	T1DM, T2DM	18	8.6 (range 7.4-9.7) (preconception) 7.1 (range 6.2-8.0) (T2) 7.0 (range 6.7-9.4) (T3)	1 (5.6)	N/A	N/A	N/A
Mathiesen/ Hod*[57,58]	RCT	T1DM	152 Detemir	6.27 (T3)	25 (16)	1.1	96.8	N/A
			158 NPH	6.33 (T3)	33 (21)	1.2	113.8 p=0.012	

Table Continues...

Authors	Study design	Study population	Number of patients	Mean A1c (%)‡‡	Maternal hypoglycemia, n (%)	Maternal hypoglycemia (events/patient)	Fasting glucose (mg/dL)	Postprandial glucose (mg/dL)
Callesen[53]	Retrospective	T1DM	67 Detemir	6.6 (5.6-9.8) (8 wks)†	15 (23)	N/A	N/A	N/A
				6.1 (5.1-7.6) (33 wks)†				
			46 Glargine	6.8 (5.4-10.1) (8 wks)†	10 (23)	N/A	N/A	N/A
				6.2 (4.8-7.2) (33 wks)†				

Values statistically significant would be indicated with p-value

‡‡Unless otherwise specified, A1c is mean or T1 level.

*Authors reported on same study

†Values reported as median values (range)

Table 9 Neonatal outcomes with Detemir use during pregnancy

Authors	Study population	Number of patients	Macrosomia, n (%)	Birth weight (g)	Congenital malformations, n (%)	Neonatal hypoglycemia, n (%)
Lapolla[55]	T1DM	10	2 (20.0)	3538±513	0 (0)	1 (10.0)
Shenoy[56]	T1DM, T2DM	18	9 (50.0)	N/A	N/A	13 (72.2)
Mathiesen/ Hod*[57,58]	T1DM	152 Detemir	59 (46.1)	3504±645	8 (5.6)	15 (11.7)
		158 NPH	73 (53.7)	3571±601	8 (5.5)	24 (17.3)
Callesen[53]	T1DM	67 Detemir	33 (49.2)	3490 (1484-4500)†	1 (1.5)	25 (37.3)
		46 Glargine	14 (30.4) p=0.046	3219 (1829-4356)† p=0.05	1 (2.2)	19 (41.3)

Values statistically significant would be indicated with p-value

*Authors reported on same study

†Values reported as median values (range)

Discussion

Lispro

Insulin lispro has an increased affinity for insulin-like growth factor (IGF-1) receptor versus human insulin, which is concerning for potential fetal growth-stimulating effects.[59] Lispro has the potential to pass via the placenta if it forms immune complexes with immunoglobulins. However, Jovanovic et al.[20] have shown no placental transfer via umbilical blood samples following intravenous administration of lispro during labor and similarly, Holcberg et al.[60] conducted an *in vitro* perfusion study that demonstrated no lispro in the umbilical cord.[20,58,59]

The data from observational studies and small randomized trials that we have reviewed, suggest that lispro is safe to use in pregnancy. The majority of studies did not report significant differences in birth weight of neonates delivered from women having either PGDM or GDM, when comparing lispro to regular insulin exposure.

The study by Durnwald et al.[29] is the only publication we identified that demonstrated significantly greater birth weight in the lispro group versus regular insulin.[29] Similarly, Lapolla et al.[26] reported significantly higher rate of LGA infants in lispro group (55.1%) versus regular insulin (39.2%) (p<0.0267). They also found higher rate of macrosomia in the lispro group (14.5%) compared to regular insulin

(11.5%), although the increase was not significant.[26] The two meta-analysis published by Gonzalez et al.[32] and Lv et al.[33] both reported an increased rate of LGA newborns, along with increased birth weight in the latter. The earlier study only included four studies and limited to T1DM, which does not fully provide compelling evidence. The meta-analysis conducted by Lv et al.,[33] which included 24 studies with a total of 3724 women, provided stronger data to support the possibility that insulin lispro is associated with increased birth weight and rate of LGA newborns. However, this significance is not apparent with the use of insulin aspart in comparison to regular insulin. Considering larger wealth of studies on insulin lispro in pregnancy compared to aspart, the meta-anaylsis may not have been sufficiently powered to see the same effect. By contrast, the small randomized trial by Di Cianni et al.[31] reported birth weight to be significantly increased in the regular insulin group.[31] The majority of published data, however, show no difference in birth weight or rates of macrosomia or LGA infants.

There was no apparent correlation between duration of exposure to lispro and size of infants, since the rate of LGA was similar in those who continued lispro throughout pregnancy to those discontinuing during T1.[26] Lapolla et al.[26] further speculated these findings may be due to short-lived glycemic peaks of lispro, although this data was not recorded in their study.

Garcia-Dominguez et al.[30] demonstrated a significant increase in neonatal hypoglycemia with lispro use, but the authors suggested that this may have been due to concomitant use of an insulin pump.[30] The remaining data we found did not indicate there was any difference in rates of neonatal hypoglycemia between those exposed to in utero to regular insulin versus lispro.

Another concern regarding lispro comes from a case series of 3 women from Kitzmiller et al.[60] who reported the development of diabetic retinopathy.[60] However, Loukovaara et al.[23] demonstrated that lispro had no impact on the progression of diabetic retinopathy.[23] Masson et al.[17] similarly reported that none of the patients developed retinopathy de novo, but 6 patients with established retinopathy required laser therapy during pregnancy.[17] Similarly, Buchbinder et al.[21] showed no change in retinopathy status in patients using lispro, but demonstrated change in 6 patients using regular insulin (extensive proliferative retinopathy developed in one patient, mild background retinopathy developed in in 3 patients, progression of retinopathy occurred in 2 patients).[21] Persson et al.[27] showed development of proliferative retinopathy in one patient in regular insulin group and similar development of mild to moderate background retinopathy in both groups.[27]

In terms of rates of congenital malformations, none of the studies we reviewed demonstrated a difference between lispro and regular insulin use. Persson et al.[27] reported one congenital malformation with human insulin, but since randomization did not occur until 14 weeks gestation, this finding should not be attributable to treatments used in the study.[27] Also, Aydin et al.[25] demonstrated congenital anomalies in 9 infants born to women who were treated with regular insulin versus none in the lispro group, although differences were not significant.[25]

There appears to be a clear advantage of using lispro for its reduction in incidence of maternal hypoglycemia. Garcia-Dominguez et al.[30] were able to demonstrate significantly lower rates of maternal hypoglycemia in lispro group versus regular insulin.[30] Interestingly, Persson et al.[27] showed a significant increase biochemical hypoglycemia (<54mg/dL) in the lispro group, although no episodes of severe hypoglycemia were demonstrated.[27] The studies observed postprandial glycemia consistently decreased, particularly 1-hour postprandially.[12,20,27,31] Of the studies that measured fasting glycemia, there were no differences between lispro and regular insulin.[12,20,27,31]

As suggested by these results glycemic control measured by A1c was improved in lispro groups versus regular insulin in multiple studies,[22,23,26,29] except for the Garcia-Dominguez et al.[30] report showing greater A1c levels in the lispro group, p=0.022.[30]

Aspart

Unlike lispro, aspart exhibits the same affinity for IGF-1 receptor as human insulin.[6] However, only a small body of literature exists on the use of aspart in women with either PGDM or GDM. Of the smaller of the 3 randomized studies, Pettitt et al.[34] found aspart to be superior in terms of glycemic profile over 240 minutes.[34] Another report demonstrated a significant improvement of 1-hour postprandial glucose levels with aspart when compared to regular insulin, suggesting a similar advantage in the control of postprandial glycemia as is provided by lispro.[31]

A larger randomized trial reported by Mathiesen et al.[13] and Hod et al.[14] reported no difference in the incidences of major maternal hypoglycemia and congenital malformations.[13,14] Glycemic control was also comparable between groups. Aspart use resulted in greater overall treatment satisfaction and willingness to continue with the treatment, primarily due to increased flexibility of treatment. Thus, this regimen appears to facilitate treatment compliance. This may be particularly important when considering treating women with insulin, a management decision with the potential to affect disease progression and maternal and neonatal morbidity and mortality.

See the Lispro section above for the results of the meta-analysis by Lv et al.[33]

Glargine

Similar to lispro, glargine has an increased affinity for IGF-1 receptor compared to human insulin.[6] IGF-1 may have a role in the development of diabetic retinopathy, as well as development of tumors of bone, mammary and ovarian tumors, as supported by *in vitro* studies on human osteosarcoma cells showing the mitogenic potential of glargine.[7] Hence, the concern for glargine interfering with fetal development.[62] However, studies in rats and mice failed to show an increase in tumor formation with prolonged glargine exposure.[49,63] Furthermore, Pollex et al.[62] carried out an *in vitro* transplacental transfer study and demonstrated undetectable transfer of glargine at therapeutic concentrations of 150pmol/L.[64]

The studies we have reviewed that investigated glargine use during pregnancy, supports its safety with possible advantages of improved efficacy of achieving fasting and postprandial glycemic targets. In addition, our review found support for glargine-associated reduction in maternal hypoglycemia. Negrato et al.[52] demonstrated that maternal complications tended to occur in women with PGDM; these included progression of retinopathy, nephropathy, preeclampsia, proteinuria and hypoglycemia.[52] A statistically significant improvement of mean A1c change from T1 to T3 was demonstrated by Poyhonen-Alho et al.[48] All studies reviewed, reported either no difference in the rate of maternal hypoglycemia or a significantly decreased rate compared to NPH.[15,46–48,50,52,53]

The data we identified also suggest that there is no difference in neonatal outcomes, including birth weight, neonatal hypoglycemia, and the incidence of congenital malformations. With one exception, there was a significant increase in shoulder dystocia in the glargine group in findings reported by Egerman et al.[51] The authors speculated the pharmacokinetic profile of glargine may reduce the transfer of metabolic fuel across the trophoblast, although evidence to support this hypothesis is lacking.[51]

Detemir

Detemir has reduced affinity for IGF-1 receptor.[59] Its use in pregnancy has not been widely studied. The only comparative analysis published, compared maternal and neonatal outcomes to glargine.[53] Callesen et al. established comparable glycemic and pregnancy outcomes, except for significantly lower mean birth weight and incidence of LGA infants in the glargine group. This suggests that the peakless glycemic profile of glargine may confer some advantage in pregnancy.

The only randomized trial of over 300 subjects, compared detemir to NPH and found glycemic control and major hypoglycemic events to be comparable at 36 weeks' gestational age. The only statistically significant finding was a lower mean fasting glucose in the detemir group.[57,58] The limited body of data on detemir use during pregnancy thus prohibits us from drawing conclusions.

Basal-bolus therapy with rapid and long-acting insulin analogues

Umpierrez et al.[65] have demonstrated the superiority of glycemic control (regarding hyperglycemia and hypoglycemia episodes) with BBT using glargine and glulisine, over sliding-scale insulin therapy with regular insulin, in a randomized trial of 130 adults with T2DM [65]. The comparative studies we reviewed that utilized BBT comprised of rapid- and short-acting analogues with a long-acting analogue, in their treatment regimens during pregnancy, have demonstrated no significant increase in maternal and neonatal risks compared to conventional therapy.

We have identified evidence indicating that the use of rapid- and long-acting insulin analogues is safe in pregnancy. Studies have established these hypoglycemic agents do not cross the placenta.[16,59,60,64] There appears to be clinical advantages of the prenatal use of insulin analogues, such as lispro use being associated with improved levels of postprandial glucose. Timely initiation of insulin treatment to achieve preprandial glucose targets of <90mg/dL and 2-hour postprandial glucose targets of <120mg/dL, have been associated with lower risks of fetal and maternal complications.[2,4,6,7]

Studies in non-pregnant patients show that BBT compared to NPH plus regular insulin or sliding scale insulin replacement, is superior in terms of achieving glycemic targets and lower risk of severe hypoglycemia.[65] BBT is standard in non-pregnant individuals affected by T1DM or T2DM. Advantages of BBT when compared to conventional insulin therapy include the convenience of flexible pre- and post-dosing of bolus therapy with once daily dosing for basal insulin. Furthermore, the use of insulin analogues allows for stringent glycemic control during pregnancy with minimal glucose excursions throughout the day.[6] Our review provides support for use of BBT with insulin analogues when glycemic targets are not met with the use of nutrition therapy or oral hypoglycemic agents. The use of BBT during pregnancy is not only associated with improved perinatal outcomes, but it will also allow for continuing standard medical treatment from preconception until after the postpartum period. The only opposing evidence proposed by one meta-analysis suggesting that insulin lispro is associated with increased birth weight and LGA rates in newborns, while finding no other differences in any other maternal or neonatal outcome for lispro, aspart, glargine, and determir in comparison to regular and NPH insulin. While our review found a wealth of evidence to suggest otherwise, it propels us to conclude the demand for rigorous, high-quality, and sufficiently powered randomized clinical trials.

Conclusion

1. Insulin analogue use in pregnancy complicated by diabetes has been associated with decreases in A1C, less maternal and neonatal hypoglycemia, when compared to conventional insulins (regular and NPH).

2. Although these studies are inadequately powered to definitively conclude an absence of adverse effect associated with insulin analogue therapy in pregnancy, rapid- and long-acting insulin analogue therapy during pregnancy has not been associated with any adverse maternal and neonatal outcome. Further high quality and adequately powered randomized clinical trials need to be conducted to determine true associations of insulin analogues to adverse outcomes.

3. Adoption of BBT would facilitate continuity of standard insulin treatment from preconception through the postpartum periods.

Conflicts of interest

The authors declare there is no conflict of interests.

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